

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 209/48, A61K 31/40, C07D 209/46		A1	(11) International Publication Number: WO 97/23457 (43) International Publication Date: 3 July 1997 (03.07.97)
(21) International Application Number: PCT/US96/20616 (22) International Filing Date: 24 December 1996 (24.12.96) (30) Priority Data: 08/578,738 26 December 1995 (26.12.95) US (71) Applicant (for all designated States except US): CELGENE CORPORATION [US/US]; 7 Powder Horn Drive, Warren, NJ 07059 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): MULLER, George, W. [US/US]; 250 Windmill Court, Bridgewater, NJ 08807 (US). SHIRE, Mary [IE/US]; 8 Stone Street, North Plainfield, NJ 07060 (US). (74) Agent: COLLINS, Bruce, M.; Mathews, Collins, Shepherd & Gould, P.A., Suite 306, 100 Thanet Circle, Princeton, NJ 08540-3674 (US).			(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: IMIDES AS PDE III, PDE IV AND TNF INHIBITORS (57) Abstract Novel amides are inhibitors of TNF α and phosphodiesterase and can be used to combat cachexia, endotoxic shock, retrovirus replication, asthma, and inflammatory conditions. A typical embodiment is 3-phthalimido-3-(3-cyclopentyloxy-4-methoxyphenyl)propionamide.			

ATTORNEY DOCKET NUMBER: 9516-086-999
SERIAL NUMBER: 10/534,324
REFERENCE: B03

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LJ	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

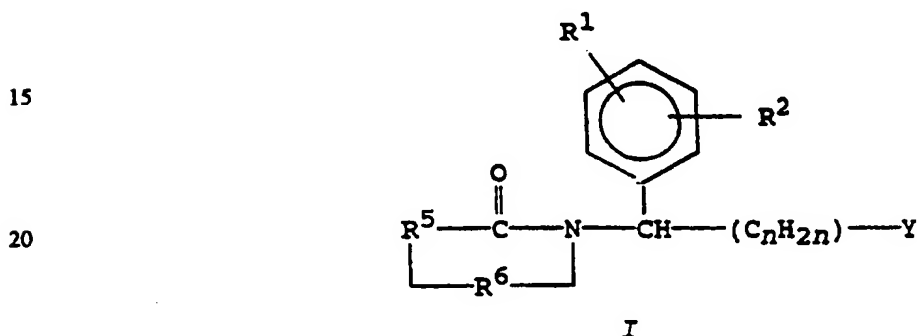
IMIDES AS PDE III, PDE IV AND TNF INHIBITORS

Cross Reference

This is a continuation-in-part of Serial No. 08/520,710
 5 filed August 29, 1995.

Detailed Description

The present invention pertains to a class of compounds which inhibit the action of phosphodiesterases, particularly PDE III and PDE IV, and the formation of tumor necrosis factor
 10 α , or TNF α , and the nuclear factor κ B, or NF κ B. These compounds can be diagrammatically represented by the formula:



in which:

25 one of R^1 and R^2 is R^3 -X- and the other is hydrogen, nitro, cyano, trifluoromethyl, carbo(lower)alkoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, lower alkyl, alkylamino, lower alkoxy, halo, HF_2CO , F_3CO or R^3 -X-;

30 R^3 is monocycloalkyl, bicycloalkyl, or benzocycloalkyl of up to 18 carbon atoms, tetrahydropyran, or tetrahydrofuran;

X is a carbon-carbon bond, $-CH_2-$, $-O-$ or $-N=$;

R^5 is: (i) o-phenylene, unsubstituted or substituted with 1 or more substituents each selected independently from nitro,

cyano, halo, trifluoromethyl, carbo(lower)alkoxy, acetyl, or carbamoyl, unsubstituted or substituted with lower alkyl, acetoxy, carboxy, hydroxy, amino, lower alkylamino, lower acylamino, lower acylamino, aminoalkyl, or lower alkoxy; (ii) 5 the vicinally divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms; (iii) a vicinally divalent cycloalkyl or cycloalkenyl of 4-10 carbon atoms, unsubstituted or substituted with 1 or more substituents each 10 selected independently from the group consisting of nitro, cyano, halo, trifluoromethyl, carbo(lower)alkoxy, acetyl, carbamoyl, acetoxy, carboxy, hydroxy, amino, lower alkylamino, lower alkyl, lower alkoxy, or phenyl; (iv) vinylene di-substituted with lower alkyl; or (v) ethylene, unsubstituted or 15 monosubstituted or disubstituted with lower alkyl;

R^6 is $-CO-$, $-CH_2-$, or $-CH_2CO-$;

Y is $-COZ$, $-C(=O)N$, $-OR^8$, lower alkyl, or aryl;

Z is $-NH_2$, $-OH$, $-NHR$, $-R^9$, or $-OR^9$;

R^8 is hydrogen or lower alkyl;

20 R^9 is lower alkyl or benzyl; and,

n has a value of 0, 1, 2, or 3.

The term alkyl as used herein denotes a univalent saturated branched or straight hydrocarbon chain. Unless otherwise stated, such chains can contain from 1 to 18 carbon 25 atoms. Representative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, tert-pentyl, hexyl, isohexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, and 30 the like. When qualified by "lower", the alkyl group will contain from 1 to 6 carbon atoms. The same carbon content

applies to the parent term "alkane" and to derivative terms such as "alkoxy".

The term cycloalkyl as used herein denotes a univalent saturated cyclic hydrocarbon chain. Unless otherwise stated, such chains can contain up to 18 carbon atoms. Monocycloalkyl refers to groups having a single ring. Polycycloalkyl denotes hydrocarbon groups having two or more ring systems having two or more ring atoms in common. Benzocycloalkyl denotes a monocyclic or polycyclic group fused to a benzo ring.

Representative of monocycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, cycloundecyl, cyclododecyl, cyclotridecyl, cyclotetradecyl, cyclopentadecyl, cyclohexadecyl, cycloheptadecyl, and cyclooctadecyl. Representative of polycycloalkyl groups are bicyclo[2.2.1]heptyl, bicyclo[3.2.1]octyl, and bicyclo[2.2.2]octyl. Benzocycloalkyl is typified by tetrahydronaphthyl, indanyl, and benzocycloheptanyl.

This invention also relates to a method of reducing the level of cytokines and their precursors in mammals and to compositions useful therein.

TNF α is a cytokine which is released primarily by mononuclear phagocytes in response to immunostimulators. When administered to animals or humans, TNF α can cause inflammation, fever, cardiovascular effects, hemorrhage, coagulation, and acute phase responses similar to those seen during acute infections and shock states.

NF κ B is a pleiotropic transcriptional activator (Lenardo, et al., Cell 1989, 58, 227-29) which has been implicated in a variety of disease and inflammatory states. NF κ B is thought to regulate cytokine levels including, but not limited to, TNF α and to be an activator of HIV transcription (Dbaibo et al., J. Biol. Chem. 1993, 17762-66; Duh et al., Proc. Natl.

Acad. Sci. 1989, 86, 5974-78; Bachelier et al., Nature 1991, 350, 709-12; Boswas et al., J. Acquired Immune Deficiency Syndrome 1993, 6, 778-786; Suzuki et al., Biochem. and Biophys. Res. Comm. 1993, 193, 277-83; Suzuki et al., Biochem. and Biophys. Res. Comm. 1992, 189, 1709-15; Suzuki et al., Biochem. Mol. Bio. Int. 1993, 31(4), 693-700; Shakhov et al., 1990, 171, 35-47; and Staal et al., Proc. Natl. Acad. Sci. USA 1990, 87, 9943-47. Thus inhibition of NF κ B binding can regulate transcription of cytokine gene(s) and through this modulation and other mechanisms is useful in the inhibition of a multitude of disease states. TNF α and NF κ B levels are influenced by a reciprocal feedback loop.

Many cellular functions which contribute to inflammatory conditions and diseases including asthma, inflammation, and other conditions are mediated by levels of adenosine 3',5'-cyclic monophosphate (cAMP). See, e.g., Lowe and Cheng, Drugs of the Future, 17(9), 799-807, 1992. It has been shown that the elevation of cAMP in inflammatory leukocytes inhibits their activation and the subsequent release of inflammatory mediators. Increased levels of cAMP also leads to the relaxation of airway smooth muscle. The primary cellular mechanism for the inactivation of cAMP is the breakdown of cAMP by a family of isoenzymes referred to as cyclic nucleotide phosphodiesterases (PDE), of which seven are known. It is recognized, for example, that the inhibition of PDE type IV is particularly effective in both the inhibition of inflammatory mediator release and the relaxation of airway smooth muscle. Thus, compounds which inhibit PDE IV specifically inhibit inflammation and relax airway smooth muscle, with a minimum of unwanted side effects such as cardiovascular or anti-platelet effects. It is now known that inhibition of TNF α production is a consequence of inhibition of PDE IV.

Excessive or unregulated TNF α production has been implicated in a number of disease conditions. These include endotoxemia and/or toxic shock syndrome (Tracey et al., Nature

330, 662-664 (1987) and Hinshaw et al., Circ. Shock 30, 279-292 (1990)); cachexia (Dezube et al., Lancet, 335 (8690), 662 (1990)); and Adult Respiratory Distress Syndrome where TNF α concentration in excess of 12,000 pg/milliliters have been
5 detected in pulmonary aspirates from ARDS patients (Millar et al., Lancet 2 (8665), 712-714 (1989)). Systemic infusion of recombinant TNF α also resulted in changes typically seen in ARDS (Ferrai-Baliviera et al., Arch. Surg. 124(12), 1400-1405 (1989)).

10 TNF α also appears to be involved in bone resorption diseases, including arthritis where it has been determined that when activated, leukocytes will produce a bone-resorbing activity, and data suggest that TNF α contributes to this activity (Bertolini et al., Nature 319, 516-518 (1986) and
15 Johnson et al., Endocrinology 124(3), 1424-1427 (1989)). It has been determined that TNF α stimulates bone resorption and inhibits bone formation in vitro and in vivo through stimulation of osteoclast formation and activation combined with inhibition of osteoblast function. Although TNF α may be
20 involved in many bone resorption diseases, including arthritis, the most compelling link with disease is the association between production of TNF α by tumor or host tissues and malignancy associated hypercalcemia (Calci. Tissue Int. (US) 46 (Suppl.), S3-10 (1990)). In Graft versus Host Disease,
25 increased serum TNF α levels have been associated with major complications following acute allogenic bone marrow transplants (Holler et al., Blood, 75(4), 1011-1016 (1990)).

Cerebral malaria is a lethal hyperacute neurological syndrome associated with high blood levels of TNF α and the most
30 severe complication occurring in malaria patients. Levels of serum TNF α correlated directly with the severity of the disease and the prognosis in patients with acute malaria attacks (Grau et al., N. Engl. J. Med. 320 (24), 1586-1591 (1989)).

TNF α also appears to play a role in the area of chronic pulmonary inflammatory diseases. The deposition of silica particles leads to silicosis, a disease of progressive respiratory failure caused by a fibrotic reaction. Antibodies to TNF α completely blocked the silica-induced lung fibrosis in mice (Pignet et al., Nature, 344:245-247 (1990)). High levels of TNF α production (in the serum and in isolated macrophages) have been demonstrated in animal models of silica and asbestos induced fibrosis (Bissonnette et al., Inflammation 13(3), 329-339 (1989)). Alveolar macrophages from pulmonary sarcoidosis patients also have been found to release spontaneously massive quantities of TNF α , as compared with macrophages from normal donors (Baughman et al., J. Lab. Clin. Med. 115 (1), 36-42 (1990)).

TNF α is also implicated in the inflammatory response which follows reperfusion (reperfusion injury) and is a major cause of tissue damage after loss of blood flow (Vedder et al., PNAS 87, 2643-2646 (1990)). TNF α also alters the properties of endothelial cells and has various pro-coagulant activities, such as producing an increase in tissue factor pro-coagulant activity and suppression of the anticoagulant protein C pathway as well as down-regulating the expression of thrombomodulin (Sherry et al., J. Cell Biol. 107, 1269-1277 (1988)). TNF α has pro-inflammatory activities which together with its early production (during the initial stage of an inflammatory event) make it a likely mediator of tissue injury in several important disorders including but not limited to, myocardial infarction, stroke and circulatory shock. Of specific importance may be TNF α -induced expression of adhesion molecules, such as intercellular adhesion molecule (ICAM) or endothelial leukocyte adhesion molecule (ELAM) on endothelial cells (Munro et al., Am. J. Path. 135 (1), 121-132 (1989)).

Moreover, it is now known that TNF α is a potent activator of retrovirus replication including activation of HIV-1 (Duh et al., Proc. Nat. Acad. Sci. 86, 5974-5978 (1989); Poll et al., Proc. Nat. Acad. Sci. 87, 782-785 (1990); Monto et al.,

Blood 79, 2670 (1990); Clouse et al., J. Immunol. 142, 431-438 (1989); Poll et al., AIDS Res. Hum. Retrovirus, 191-197 (1992)). AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Other viruses, such as HIV-1 and HIV-2, infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication. Cytokines, specifically TNF α , are implicated in activated T-cell mediated HIV protein expression and/or virus replication in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by prevention or inhibition of cytokine production, notably TNF α , in a HIV-infected individual aids in limiting the maintenance of T lymphocyte activation caused by HIV infection.

Monocytes, macrophages, and related cells, such as kupfer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells (Rosenberg et al., The Immunopathogenesis of HIV Infection, Advances in Immunology, 57 (1989)). Cytokines, such as TNF α , have been shown to activate HIV replication in monocytes and/or macrophages (Poli et al., Proc. Natl. Acad. Sci., 87, 782-784 (1990)), therefore, prevention or inhibition of cytokine production or activity aids in limiting HIV progression as stated above for T cells. Additional studies have identified TNF α as a common factor in the activation of HIV in vitro and has provided a clear mechanism of action via a nuclear regulatory protein found in the cytoplasm of cells (Osborn, et al., PNAS

86, 2336-2340). This evidence suggests that a reduction of TNF α synthesis may have an antiviral effect in HIV infections, by reducing the transcription and thus virus production.

5 AIDS viral replication of latent HIV in T cell and macrophage lines can be induced by TNF α (Folks et al., PNAS 86, 2365-2368 (1989)). A molecular mechanism for the virus inducing activity is suggested by TNF α 's ability to activate a gene regulatory protein (NF κ B) found in the cytoplasm of cells, which promotes HIV replication through binding to a
10 viral regulatory gene sequence (LTR) (Osborn et al., PNAS 86, 2336-2340 (1989)). TNF α in AIDS associated cachexia is suggested by elevated serum TNF α and high levels of spontaneous TNF α production in peripheral blood monocytes from patients (Wright et al., J. Immunol. 141 (1), 99-104 (1988)).

15 TNF α has been implicated in other viral infections, such as the cytomegalia virus (CMV), influenza virus, adenovirus, and the herpes family of viruses for similar reasons as those noted.

It is recognized that suppression of the effects of TNF α
20 can be beneficial in a variety of conditions and in the past, steroids such as dexamethasone and prednisolone as well as polyclonal and monoclonal antibodies (Beutler et al., Science 234, 470-474 (1985); WO 92/11383) have been employed for this purpose. Conditions in which inhibition of TNF α or NF κ B is
25 desirable include septic shock, sepsis, endotoxic shock, hemodynamic shock and sepsis syndrome, post ischemic reperfusion injury, malaria, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic disease, cachexia, graft rejection, cancer, autoimmune
30 disease, opportunistic infections in AIDS, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and other arthritic conditions, Crohn's disease, ulcerative colitis, multiple sclerosis, systemic lupus erythrematosis, ENL in leprosy, radiation damage, and hyperoxic alveolar injury.

The compounds can be used, under the supervision of qualified professionals, to inhibit the undesirable effects of TNF α , NF κ B, or phosphodiesterase. The compounds can be administered orally, rectally, or parenterally, alone or in
5 combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment. Oral dosage forms include tablets, capsules, dragees, and similar shaped, compressed pharmaceutical forms. Isotonic saline solutions containing 20-100 milligrams/milliliter can
10 be used for parenteral administration which includes intramuscular, intrathecal, intravenous and intra-arterial routes of administration. Rectal administration can be effected through the use of suppositories formulated from conventional carriers such as cocoa butter.

15 Dosage regimens must be titrated to the particular indication, the age, weight, and general physical condition of the patient, and the response desired but generally doses will be from about 1 to about 1000 milligrams/day as needed in single or multiple daily administration. In general, an initial
20 treatment regimen can be copied from that known to be effective in interfering with TNF α activity for other TNF α mediated disease states by the compounds of the present invention. Treated individuals will be regularly checked for T cell numbers and T4/T8 ratios and/or measures of viremia
25 such as levels of reverse transcriptase or viral proteins, and/or for progression of cytokine-mediated disease associated problems such as cachexia or muscle degeneration. If no effect is observed following the normal treatment regimen, then the amount of cytokine activity interfering agent
30 administered is increased, e.g., by fifty percent a week.

The compounds of the present invention can also be used topically in the treatment or prophylaxis of topical disease states mediated or exacerbated by excessive TNF α production, such as viral infections, for example those caused by the
35 herpes viruses or viral conjunctivitis, psoriasis, other skin disorders and diseases, etc.

The compounds can also be used in the veterinary treatment of mammals other than humans in need of prevention or inhibition of TNF α production. TNF α mediated diseases for treatment, therapeutically or prophylactically, in animals
5 include disease states such as those noted above, but in particular viral infections. Examples include feline immunodeficiency virus, equine infectious anaemia virus, caprine arthritis virus, visna virus, and maedi virus, as well as other lentiviruses.

10 The compounds of this invention possess at least one center of chirality, that to which the depicted phenyl group is attached, and thus will exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereoisomers when there are two or
15 more chiral centers, are within the scope of the present invention. The racemates can be used as such or can be separated into their individual isomers mechanically as by chromatography using a chiral absorbent. Alternatively, the individual isomers can be prepared in chiral form or separated
20 chemically from a mixture by forming salts with a chiral acid, such as the individual enantiomers of 10-camphorsulfonic acid, camphoric acid, alpha-bromocamphoric acid, methoxyacetic acid, tartaric acid, diacetyltartaric acid, malic acid, pyrrolidone-5-carboxylic acid, and the like, and then freeing one or both
25 of the resolved bases, optionally repeating the process, so as to obtain either or both isomers substantially free of the other; i.e., in a form having an optical purity of >95%.

Inhibition of production of TNF α by these compounds can be conveniently assayed using methods known in the art. For
30 example, TNF α Inhibition Assays can be determined by a variety of known methods.

PBMC from normal donors is obtained by Ficoll-Hypaque density centrifugation. Cells are cultured in RPMI supplemented with 10% AB+ serum, 2mM L-glutamine, 100 U/mL penicillin and 100 mg/mL streptomycin. The active compound is
35

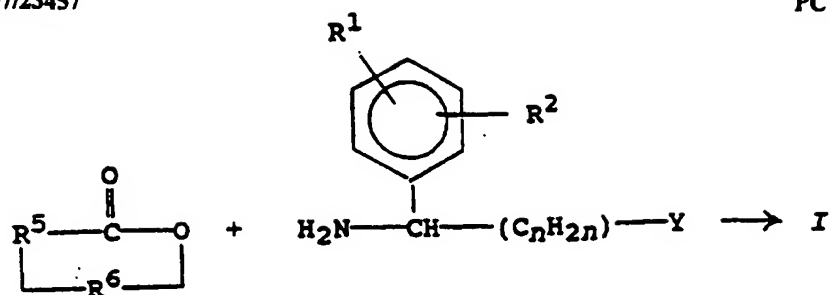
dissolved in DMSO (Sigma Chemical) and further dilutions are done in supplemented RPMI. The final DMSO concentration in the presence or absence of drug in the PBMC suspensions is 0.25 wt %. Test candidates are assayed at half-log dilutions
5 starting at 50 mg/mL, being added to PBMC (10^6 cells/mL) in 96 wells plates one hour before the addition of LPS. PBMC (10^6 cells/mL) in the presence or absence of the compound is stimulated by treatment with 1 mg/mL of LPS from Salmonella minnesota R595 (List Biological Labs, Campbell, CA). Cells
10 are then incubated at 37°C for 18-20 hours. The supernatants then are harvested and assayed immediately for TNF α levels or frozen at -70°C (for not more than 4 days) until assayed. The concentration of TNF α in the supernatant is determined by human TNF α ELISA kits (ENDOGEN, Boston, MA) according to the
15 manufacturer's directions.

Particularly preferred are compounds in which R⁵ is o-unsubstituted or substituted phenylene, R¹ is lower alkoxy, R³ is monocycloalkyl of up to 10 carbon atoms, R⁶ is -CO- or -CH₂-, Y is lower alkyl, -COZ or -CPN, Z is -NH₂, -OH, or -
20 O(lower alkyl), and n has a value of 0 or 1.

The compounds of the present invention can be prepared using methods known per se. For example, a cyclic acid anhydride or a lactone is allowed to react with the appropriate disubstituted phenyl compound:

5

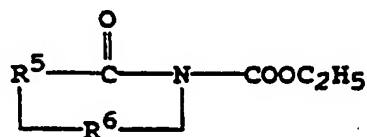
10



in which R^1 , R^2 , R^5 , R^6 , Y , and n are as defined above. The reaction can be effected simply by heating, analogously to the methods described in U.K. Patent Specification No. 1,036,694, the disclosure of which is incorporated herein by reference. Optionally acetic acid, with or without sodium acetate, can be added.

In place of the acid anhydride or lactone, one can utilize an N-carbethoxy derivative of the formula:

20



25

In a further embodiment, compounds in which R^6 is $-\text{CH}_2-$ can be formed through condensation of a dialdehyde with a disubstituted phenyl compound in the presence of refluxing acetic acid utilizing the method of Griggs et al., J. Chem. Soc., Chem. Comm., 1985, 1183-1184, the disclosure of which is incorporated herein by reference.

The disubstituted phenyl starting materials can be obtained through condensation of an appropriately substituted aldehyde and malonic acid, with intermediate formation of the phenyl amidine and subsequent decarboxylation.

The disubstituted aldehydes can be prepared utilizing classical methods for ether formation; e.g., reaction with the appropriate bromide in the presence of potassium carbonate. Numerous cycloalkyloxy benzaldehydes and procedures for

preparing them are described in the literature. See, e.g., Ashton et al., J. Med. Chem., 1994, 37, 1696-1703; Saccomano et al., J. Med. Chem., 1994, 34, 291-298; and Cheng et al., Org. and Med. Chem. Lett., 1995, 5(17), 1969-1972, the disclosures of which are incorporated herein by reference.

Representative starting materials include 3-cyclopentyloxy-4-methoxybenzaldehyde, 3-cyclopentyloxy-4-ethoxybenzaldehyde, 3-cyclohexyloxy-4-methoxybenzaldehyde, 3-(exo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzaldehyde, 3-(endo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzaldehyde, 3-(bicyclo[2.2.2]oct-2-yloxy)-4-methoxybenzaldehyde, 3-(bicyclo[3.2.1]oct-2-yloxy)-4-methoxybenzaldehyde, 3-indan-2-yloxy-4-methoxybenzaldehyde, and 3-(endo-benzobicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzaldehyde.

The following examples will serve to further typify the nature of this invention but should not be construed as a limitation in the scope thereof, which scope is defined solely by the appended claims.

Example 1

3-Amino-3-(3-cyclopentyloxy-4-methoxyphenyl)propionic Acid

A stirred suspension of 3-cyclopentyloxy-4-methoxybenzaldehyde (10.0 g, 45.4 mmol) and ammonium acetate (7.00 g, 90.8 mmol) in ethanol (95%, 30 mL) under nitrogen was heated to 45-50°C and malonic acid (4.72 g, 45.4 mmol) was added. The solution was heated at reflux for 24 hours. The mixture was allowed to cool to room temperature and was then filtered. The solid which is collected was washed with ethanol, air dried and then dried in vacuo (60°C, < 1 mm) to afford 7.36 g (58%) of the product: mp 225-226°C; ¹H NMR (D₂O/NaOH/TSP) δ 7.05-6.88 (m, 3H), 4.91-4.78 (m, 1H), 4.21-4.14 (m, 1H), 3.79 (s, 3H), 2.59-2.46 (m, 2H), 2.05-1.48 (m, 8H). Trace impurity peaks were present at 6.39 and 7.34 ppm. ¹³C NMR

(D₂O/NaOD/TSP) δ 182.9, 150.7, 149.1, 140.6, 121.6, 116.0, 114.9, 83.9, 58.5, 55.3, 49.8, 34.9, 26.3.

Similarly prepared from 3-cyclopentyloxy-4-methoxybenzaldehyde, 3-cyclopentyloxy-4-ethoxybenzaldehyde, and 3-cyclohexyloxy-4-methoxybenzaldehyde are 3-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)propionic acid, 3-amino-3-(3-cyclopentyloxy-4-ethoxyphenyl)propionic acid, and 3-amino-3-(3-cyclohexyloxy-4-methoxyphenyl)propionic acid, respectively.

Example 2

10 3-Phthalimido-3-(3-cyclopentyloxy-4-methoxyphenyl)propionic Acid

To a stirred mixture of 3-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)propionic acid (2.34 g, 8.40 mmol) and sodium carbonate (0.96 g, 9.05 mmol) in a mixture of water (20 mL) and acetonitrile (20 mL) under nitrogen was added N-carbethoxyphthalimide (1.9 g, 8.4 mmol). After 3 hours, the acetonitrile was removed in vacuo. The pH of the solution was adjusted to 1 with aqueous hydrogen chloride (4 N). Ether (5 mL) was added and the mixture stirred for 1 hour. The resulting slurry was filtered and the solid washed with water, air dried and then dried in vacuo (60°C, < 1 mm) to afford 2.92 g (85%) of the product as a white solid: mp 159-162°C; ¹H NMR (DMSO-d₆) δ 12.40 (br s, 1H), 7.96-7.80 (m, 4H), 7.02 (s, 1H), 6.90 (s, 2H), 5.71-5.52 (m, 1H), 4.81-4.65 (m, 1H), 3.70 (s, 3H), 3.59-3.16 (m, 2H), 2.00-1.44 (m, 8H); ¹³C NMR (DMSO-d₆) δ 171.7, 167.6, 149.1, 146.8, 134.6, 131.2, 131.1, 123.1, 119.4, 113.9, 112.1, 79.5, 55.5, 50.1, 36.1, 32.1, 32.1, 23.5; Anal. Calcd for C₂₃H₂₃NO₆. Theoretical: C, 67.47; H, 5.66; N, 3.42. Found: C, 67.34; H, 5.59; N, 3.14.

30 Similarly prepared are 3-phthalimido-3-(3-cyclopentyloxy-4-methoxyphenyl)propionic acid, 3-phthalimido-3-(3-cyclopentyloxy-4-ethoxyphenyl)propionic acid, 3-phthalimido-3-(3-cyclohexyloxy-4-methoxyphenyl)propionic acid, 3-phthalimido-3-(3-(bicyclo[3.2.1]oct-2-yloxy)-4-methoxyphenyl)propionic acid,

3-phthalimido-3-(3-indan-2-yloxy-4-methoxyphenyl)propionic acid, and 3-phthalimido-3-(3-(endo-benzobicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionic acid.

Example 3

5 3-Phthalimido-3-(3-cyclopentyloxy-4-methoxyphenyl)propionamide

A mixture of 3-phthalimido-3-(3-cyclopentyloxy-4-methoxyphenyl)propionic acid (2.05 g, 5.00 mmol), 1,1'-carbonyl-diimidazole (0.91 g, 5.5 mmol) and 4-dimethylaminopyridine (trace) in tetrahydrofuran (20 mL) was stirred for 1.5 hours under nitrogen at approximately 25°C. To the solution was added ammonium hydroxide (1.07 mL, 16.0 mmol, 28-30%) and stirring was continued for 1.5 hours. A small amount of solid forms during this time. The mixture was concentrated to half its volume and a white solid precipitated. The mixture was filtered, washed with a small amount of tetrahydrofuran, air dried, and dried in vacuo (60°C, < 1 mm) to afford 1.27 g of the product. The product was further purified by flash column chromatography (silica gel, 5% methanol/methylene chloride) and the resulting white solid was dried in vacuo (60°C, < 1 mm) to afford 1 g (49%) of the product: mp 165-166°C; ¹H NMR (CDCl₃) δ 7.85-7.61 (m, 4H), 7.16-7.04 (m, 2H), 6.85-6.75 (m, 1H), 5.80 (dd, J = 5.8, 10.4 Hz, 1H), 5.66 (br s, 1H), 5.54 (br s, 1H), 4.82-4.70 (m, 1H), 3.80 (s, 3H), 3.71 (dd, J = 10.4, 15 Hz, 1H), 3.06 (dd, J = 5.8, 15 Hz, 1H), 2.06-1.51 (m, 8H); ¹³C NMR (CDCl₃) δ 171.8, 168.3, 149.8, 147.7, 133.9, 131.8, 131.3, 123.3, 119.9, 114.6, 111.8, 80.4, 56.0, 51.6, 37.9, 32.7, 24.1; Anal. Calcd for C₂₃H₂₄N₂O₅. Theoretical: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.25; H, 5.76; N, 6.68.

Similarly prepared are 3-phthalimido-3-(3-cyclopentyloxy-4-methoxyphenyl)propionamide, 3-phthalimido-3-(3-cyclopentyloxy-4-ethoxyphenyl)propionamide, 3-phthalimido-3-(3-cyclohexyloxy-4-methoxyphenyl)propionamide, 3-phthalimido-3-(3-(endo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)-propionamide, 3-phthalimido-3-(3-(bicyclo[2.2.2]oct-2-yloxy)-

4-methoxyphenyl)propionamide, 3-phthalimido-3-(3-(bicyclo-
[3.2.1]oct-2-yloxy)-4-methoxyphenyl)propionamide, 3-phthal-
imido-3-(3-indan-2-yloxy-4-methoxyphenyl)propionamide, and 3-
phthalimido-3-(3-(endo-benzobicyclo[2.2.1]hept-2-yloxy)-4-
5 methoxyphenyl)propionamide.

Example 4

Methyl 3-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)propionate

To a cooled (ice bath temperature) and stirred mixture of
3-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)propionic acid
10 (3.00 g, 10.7 mmol) in methanol (20 mL) under nitrogen was
added thionyl chloride (1.8 mL, 2.3 mmol) dropwise via
syringe. The resulting solution was stirred at 0°C for 1
hour, the ice bath was removed and stirring was continued at
RT for 1 hour and a white solid precipitated. The methanol
15 was removed and the solid was slurried in hexane. The mixture
was filtered and the white solid was washed with hexane, air
dried and then dried in vacuo (60°C, < 1 mm) to afford 2.69 g
(76%) of the product as the hydrochloride salt: mp 183-
184.5°C; ¹H NMR (DMSO-d₆) δ 8.76 (br s, 3H), 7.25 (s, 1H),
20 7.06-6.89 (m, 2H), 4.85-4.75 (m, 1H), 4.58-4.44 (m, 1H), 3.74
(s, 3H), 3.55 (s, 3H), 3.31-2.86 (m, 2H), 2.06-1.44 (m, 8H);
¹³C NMR (DMSO-d₆) δ 169.1, 149.3, 146.5, 128.4, 119.5, 113.5,
111.4, 79.0, 55.0, 51.2, 50.3, 38.2, 31.7, 31.6, 23.0; Anal.
Calcd for C₁₆H₂₄ClNO₄. Theoretical: C, 58.27; H, 7.33; N,
25 4.25. Found: C, 58.44; H, 7.34; N, 4.13.

Similarly prepared are methyl 3-amino-3-(3-cyclo-
pentyloxy-4-methoxyphenyl)propionate, methyl 3-amino-3-(3-
cyclopentyloxy-4-ethoxyphenyl)propionate, and methyl 3-amino-
3-(3-cyclohexyloxy-4-methoxyphenyl)propionate, all as the
30 hydrochloride.

Example 5**Methyl_3-phthalimido-3-(3-cyclopentyloxy-4-methoxyphenyl)propionate**

To a stirred solution of methyl 3-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)propionate hydrochloride (0.50 g, 1.52 mmol) and sodium carbonate (0.16 g, 1.52 mmol) in a mixture of water (5 mL) and acetonitrile (5 mL) under nitrogen was added N-carbethoxyphthalimide (0.34 g, 1.52 mmol). The solution was stirred for 3 hours at RT. The acetonitrile was removed in vacuo which afforded a two layer mixture which was extracted with methylene chloride (3 x 15 mL). The combined organic extracts were dried over magnesium sulfate, filtered and then concentrated in vacuo to afford 0.77 g of the crude product as an oil. The crude product was purified by flash column chromatography (silica gel, 35/65, ethyl acetate/hexane) the resulting glassy solid was dried in vacuo to afford 0.48 g (75%) of the product as a white solid: mp 76-78°C; ¹H NMR (CDCl₃) δ 7.86-7.60 (m, 4H), 7.19-7.00 (m, 2H), 6.88-6.72 (m, 1H), 5.84-5.67 (m, 1H), 4.85-4.70 (m, 1H), 3.80 (s, 3H), 3.80-3.69 (m, 1H), 3.63 (s, 3H), 3.34-3.15 (m, 1H), 2.10-1.48 (m, 8H); ¹³C NMR (CDCl₃) δ 171.0, 168.0, 149.8, 147.6, 133.9, 131.8, 130.9, 123.2, 120.1, 114.6, 111.7, 80.4, 55.9, 51.8, 50.7, 35.9, 32.7, 24.0; Anal. Calcd for C₂₄H₂₅NO₆. Theoretical: C, 68.03; H, 5.95; N, 3.31. Found: C, 67.77; H, 5.97; N, 3.20.

Similarly prepared are methyl 3-phthalimido-3-(3-cyclopentyloxy-4-methoxyphenyl)propionate, methyl 3-phthalimido-3-(3-cyclopentyloxy-4-ethoxyphenyl)propionate, and methyl 3-phthalimido-3-(3-cyclohexyloxy-4-methoxyphenyl)propionate.

30

Example 6**3-Amino-3-(3-(exo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionic Acid**

A stirred suspension of 3-(exo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzaldehyde (6.00 g, 24.4 mmol) and ammonium

acetate (3.76 g, 48.8 mmol) in ethanol (95%, 20 mL) under nitrogen was heated to 45-50°C and malonic acid (2.53 g, 24.4 mmol) was added. The solution was refluxed for 24 hours, allowed to cool to room temperature, and filtered. The solid
5 was washed with ethanol, air dried, and dried in vacuo (60°C, < 1 mm) to afford 3.17 g (43%) of the product: mp 225-226°C; ¹H NMR (D₂O/NaOD/TSP) δ 7.09-6.90 (m, 3H), 4.41-4.28 (m, 1H), 4.27-4.15 (m, 1H), 3.82 (s, 3H), 2.64-2.48 (m, 2H) 2.44 (s, 1H), 2.31 (s, 1H), 1.92-1.76 (m, 1H), 1.69-1.38 (m, 4H), 1.30-
10 1.05 (m, 3H).

Similarly prepared from 3-(endo-bicyclo[2.2.1]hept-2-yl-oxy)-4-methoxybenzaldehyde, 3-(bicyclo[2.2.2]oct-2-yloxy)-4-methoxybenzaldehyde, 3-(bicyclo[3.2.1]oct-2-yloxy)-4-methoxybenzaldehyde, 3-indan-2-yloxy-4-methoxybenzaldehyde, and 3-
15 (endo-benzobicyclo[2.2.1]hept-2-yloxy)-4-methoxybenzaldehyde are 3-amino-3-(3-(endo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionic acid, 3-amino-3-(3-(bicyclo[2.2.2]oct-2-yloxy)-4-methoxyphenyl)propionic acid, 3-amino-3-(3-(bicyclo[3.2.1]oct-2-yloxy)-4-methoxyphenyl)propionic acid, 3-
20 amino-3-(3-indan-2-yloxy-4-methoxyphenyl)propionic acid, and 3-amino-3-(3-(endo-benzobicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionic acid, respectively.

Example 7

Methyl 3-Amino-3-(3-(exo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionate Hydrochloride

To an ice bath cooled stirred suspension of 3-amino-3-(3-(exo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionic acid (2.00 g, 6.55 mmol) in methanol (15 mL) under nitrogen was added thionyl chloride (1.56 mL, 13.1 mmol) dropwise via
30 syringe. The resulting solution was stirred at 0°C for 30 minutes, the ice bath was removed and stirring was continued at room temperature for 2.5 hours. The methanol was removed and the solid slurried in hexane (15 mL). The mixture was filtered and the white solid washed with hexane, air dried and
35 then dried in vacuo (60°C, < 1 mm) to afford 1.97 g (85%) of

the product: mp 197.5-201.5°C; ¹H NMR (DMSO-d₆) δ 7.50 (br s, 3H), 7.18 (s, 1H), 7.07-6.88 (m, 2H), 4.56-4.42 (m, 1H), 4.30-4.19 (m, 1H), 3.74 (s, 3H), 3.54 (s, 3H), 3.41-2.85 (m, 3H), 2.37 (s, 1H), 2.27 (s, 1H), 1.92-1.75 (m, 1H), 1.64-1.03 (m, 6H); ¹³C NMR (DMSO-d₆) δ 169.4, 149.6, 146.4, 128.8, 120.0, 119.9, 113.8, 111.8, 80.1, 79.9, 55.5, 51.6, 50.7, 40.5, 39.2, 38.6, 34.8, 27.8, 23.7, 23.6.

Similarly prepared are methyl 3-amino-3-(3-(endo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionate, methyl 3-amino-3-(3-(bicyclo[2.2.2]oct-2-yloxy)-4-methoxyphenyl)propionate, methyl 3-amino-3-(3-(bicyclo[3.2.1]oct-2-yloxy)-4-methoxyphenyl)propionate, methyl 3-amino-3-(3-indan-2-yloxy-4-methoxyphenyl)propionate, and methyl 3-amino-3-(3-(endo-benzobicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionate.

15

Example 8

By following the procedure of Example 3 but substituting 3-phthalimido-3-(3-(exo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionic acid, there is obtained 3-phthalimido-3-(3-(exo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionamide.

20

Similarly prepared are 3-phthalimido-3-(3-(endo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionamide, 3-phthalimido-3-(3-(bicyclo[2.2.2]oct-2-yloxy)-4-methoxyphenyl)propionamide, 3-phthalimido-3-(3-(bicyclo[3.2.1]oct-2-yloxy)-4-methoxyphenyl)propionamide, 3-phthalimido-3-(3-indan-2-yloxy-4-methoxyphenyl)propionamide, and 3-phthalimido-3-(3-(endo-benzobicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionamide.

25

Example 9

Methyl 3-Phthalimido-3-(3-(exo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionate

30

To a stirred solution of methyl 3-amino-3-(3-(exo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionate hydrochlor-

ide (1.00 g, 2.81 mmol) and sodium carbonate (0.3 g, 2.8 mmol) in a mixture of water (10 mL) and acetonitrile (10 mL) under nitrogen was added N-carbethoxyphthalimide (0.64 g, 2.81 mmol). The solution was stirred for 3 hours at room temperature. The acetonitrile was removed in vacuo and the residue extracted with methylene chloride (3 x 30 mL). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated in vacuo to afford 1.44 g of the product. The product was further purified by flash column chromatography (silica gel, 20%, ethyl acetate/methylene chloride) to afford a white solid which was then dried in vacuo to afford 0.23 g (18%) of product: mp 47-48°C; ¹H NMR (CDCl₃) δ 7.86-7.61 (m, 4H), 7.14-7.00 (m, 2H), 6.82-6.74 (m, 1H), 5.75 (dd, J = 5.9, 10 Hz, 1H), 4.25-4.14 (m, 1H), 3.84-3.69 (m, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 3.23 (dd, J = 5.9, 16.5 Hz, 1H), 2.51-2.41 (m, 1H), 2.34-2.24 (m, 1H), 1.86-1.06 (m, 8H); ¹³C NMR (CDCl₃) δ 171.1, 168.1, 149.7, 147.2, 133.9, 131.8, 130.9, 123.3, 120.1, 120.0, 114.5, 114.4, 111.8, 81.1, 56.0, 51.9, 50.8, 41.1, 41.0, 39.9, 39.8, 35.9, 35.5, 35.3, 28.4, 24.3; HPLC 97%; Anal. Calcd for C₂₆H₂₇NO₆. Theoretical: C, 69.47; H, 6.05; N, 3.12. Found: C, 69.22; H, 5.91; N, 2.95.

Similarly prepared are methyl 3-phthalimido-3-(3-(endo-bicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionate, methyl 3-phthalimido-3-(3-(bicyclo[2.2.2]oct-2-yloxy)-4-methoxyphenyl)propionate, methyl 3-phthalimido-3-(3-(bicyclo[3.2.1]oct-2-yloxy)-4-methoxyphenyl)propionate, methyl 3-phthalimido-3-(3-indan-2-yloxy-4-methoxyphenyl)propionate, and methyl 3-phthalimido-3-(3-(endo-benzobicyclo[2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionate.

Example 10

1-(3-Cyclopentoxy-4-methoxyphenyl)propylamine

To an ice bath cooled stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (2.5 M, 4.1 mL, 19.5 mmol) in tetrahydrofuran (5 mL) under nitrogen, was added a hexane

solution of butyl lithium (7.2 mL, 18 mmol) via syringe. The ice bath was removed and the solution was stirred for 30 minutes at room temperature. This solution then was added dropwise to an ice bath cooled solution of 3-cyclopentoxy-4-methoxybenzaldehyde (3.3 g, 15 mmol) in tetrahydrofuran (5mL) and the mixture stirred for 20 minutes. An ethereal solution of ethylmagnesium bromide (3 M, 10 mL, 30 mmol) then was added dropwise. The reaction solution was allowed to reach room temperature and then was stirred at room temperature. The reaction progress was monitored by HPLC (Waters Nova-Pak/EC 18 column, 3.9 x 150mm, 4micron, 1mL/min, 240nm, 35/65, CH₃CN/0.1% H₃PO₄(aq)) and after 3 hours no starting material remained. The reaction mixture was slowly poured into a saturated solution of ammonium chloride (100 mL). The resulting mixture was extracted with methylene chloride (3 x 20 mL) and the combined extracts were dried over magnesium sulfate and concentrated in vacuo to yield 5.6 g of product which was further purified by flash column chromatography (silica gel, 250/10/1, methylene chloride/methanol/ammonium hydroxide) to afford 2.5 g (67%) of the product as an oil: ¹H NMR (CDCl₃) _ 6.91-6.77 (m, 3H), 4.85-4.74 (m, 1H), 3.83 (s, 3H), 3.74 (t, J = 6.8 Hz, 1H), 2.02-1.15 (m, 12H), 0.86 (t, J = 7.4 Hz, 3H); ¹³C NMR (CDCl₃) _ 148.8, 147.5, 138.8, 118.4, 113.3, 111.8, 80.3, 57.4, 56.0, 32.7, 32.4, 10.9.

25

Example 11**3-Phthalimido-3-(3-cyclopentoxy-4-methoxyphenyl)propane**

To a stirred solution of 1-(3-cyclopentoxy-4-methoxyphenyl)propylamine (1 g, 4 mmol) and sodium carbonate (0.42 g, 4.0 mmol) in a mixture of water (5 mL) and acetonitrile (5 mL) under nitrogen was added N-carbethoxyphthalimide (0.9 g, 4.0 mmol). The solution was stirred for 2.5 hours at room temperature. The acetonitrile was removed in vacuo which resulted in the precipitation of a white solid. The mixture was filtered and the solid was washed with water, air dried and then dried in vacuo to afford 1.25 g (83%) of product: mp 100.0-102.5°C; ¹H NMR (CDCl₃) _ 7.87-

7.61 (m, 4H), 7.21-7.01 (m, 2H), 6.85-6.75 (m, 1H), 5.15 (dd, $J = 7, 9.3$ Hz, 1H), 4.86-4.74 (m, 1H), 3.81 (s, 3H), 2.66-2.20 (m, 2H), 2.08-1.47 (m, 8H), 0.95 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (CDCl_3) - 168.4, 149.4, 147.5, 133.8, 132.2, 131.9, 123.1, 120.5, 115.0, 111.5, 80.3, 55.6, 55.9, 32.7, 24.4, 11.6; HPLC (Waters Nova-Pak/EC 18 column, 3.9 x 150mm, 4micron, 1mL/min, 240nm, 60/40, $\text{CH}_3\text{CN}/0.1\% \text{H}_3\text{PO}_4(\text{aq})$) 12 min, 99%; Anal. Calcd for $\text{C}_{23}\text{H}_{25}\text{NO}_4$. Theoretical: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.72; H, 6.69; N, 3.65.

10

Example 12**1-(3-Indanyloxy-4-methoxyphenyl)propylamine**

To an ice bath cooled stirred solution of 1,1,1,3,3,3-hexamethyldisilazane (2.7 mL, 13 mmol) in tetrahydrofuran (5 mL) under nitrogen, was added a hexane solution of butyl lithium (2.5 M, 4.8 mL, 12 mmol) via syringe. The ice bath was removed and the solution was stirred for 25 minutes at room temperature. This solution then was added dropwise to an ice bath cooled solution of 3-indanyloxy-4-methoxybenzaldehyde (2.68 g, 10.0 mmol) in tetrahydrofuran (4mL) and the mixture was stirred for one hour. An ethereal solution of ethylmagnesium bromide (3 M, 6.7 mL, 20 mmol) then was added dropwise via syringe. The reaction mixture was heated at reflux and was monitored by HPLC (Waters Nova-Pak/EC 18 column, 3.9 x 150mm, 4micron, 1mL/min, 240nm, 40/60, $\text{CH}_3\text{CN}/0.1\% \text{H}_3\text{PO}_4(\text{aq})$). After 48 hours the reaction had reached completion and was allowed to cool to room temperature. The reaction mixture then was slowly poured into a saturated solution of ammonium chloride (80 mL). The resulting mixture was extracted with methylene chloride (3 x 15 mL) and the combined extracts were dried over magnesium sulfate and concentrated to afford the product which was further purified by flash column chromatography (silica gel, 250/10/1, methylene chloride/methanol/ammonium hydroxide) to afford 0.27 g (9%) of product as an orange solid.

Example 13**1-Phthalimido-1-(3-indanyloxy-4-methoxyphenyl)propane**

To a stirred solution of 1-(3-indanyloxy-4-methoxyphenyl)propylamine (0.25 g, 0.84 mmol) and sodium carbonate (0.09 g, 0.84 mmol) in a mixture of water (2 mL) and acetonitrile (2 mL) under nitrogen was added N-carbethoxyphthalimide (0.19 g, 0.84 mmol). The solution was stirred for 4 hours at room temperature. The acetonitrile was removed in vacuo and the resulting mixture was extracted with methylene chloride (2 x 10 mL), dried over magnesium sulfate and concentrated in vacuo to afford 0.35 g of the product which was further purified by flash column chromatography (silica gel, 25/75, ethyl acetate/hexane) to afford 0.19 g (48%) of the product as a solid: mp 62°C; ¹H NMR (CDCl₃) — 7.86-7.63 (m, 4H), 7.29-7.04 (m, 6H), 6.87-6.78 (m, 1H), 5.30-5.14 (m, 2H), 3.77 (s, 3H), 3.52-3.14 (m, 4H), 2.66-2.21 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ¹³C NMR (CDCl₃) — 168.4, 149.6, 147.1, 140.7, 140.6, 133.8, 132.2, 131.8, 126.5, 124.6, 123.1, 121.2, 115.3, 111.7, 79.0, 56.5, 55.9, 39.6, 39.6, 24.4, 11.6; HPLC (Waters Nova-Pak/EC 18 column, 3.9 x 150mm, 4micron, 1mL/min, 240nm, 60/40, CH₃CN/0.1% H₃PO₄ (aq)) 12 min, 98%; Anal. Calcd for C₂₇H₂₅NO₄. Theoretical: C, 75.86; H, 5.89; N, 3.28. Found: C, 75.58; H, 5.90; N, 3.20.

Example 14**1-(1-Oxoisoindoline)-1-(3-cyclopentoxo-4-methoxyphenyl)propane**

A stirred solution of phthalic dicarboxaldehyde (0.4 g, 3 mmol) and 1-(3-cyclopentoxo-4-methoxyphenyl)propylamine (0.75 g, 3.0 mmol) in glacial acetic acid (9 mL) under nitrogen was heated at reflux for 5 minutes. The stirred reaction then was allowed to cool to room temperature and concentrated in vacuo to afford the product which was further purified by flash column chromatography on silica gel, first with 40/60 ethyl acetate/hexane and then with 15/85, ethyl acetate/methylene chloride) to afford 0.48 g (44%) of the product as a yellow oil: ¹H NMR (CDCl₃) — 7.97-7.76 (m, 1H), 7.61-7.31 (m, 3H), 7.06-6.74 (m, 3H), 5.54-5.39 (m, 1H), 4.87-4.66 (m, 1H), 4.28

(d, J = 17 Hz, 1H), 4.00 (d, J = 17 Hz, 1H), 3.82 (s, 3H), 2.25-1.45 (m, 10H), 0.99 (t, J = 7.3 Hz, 3H); ¹³C NMR (CDCl₃) _ 168.3, 149.4, 147.5, 141.1, 132.7, 132.2, 130.9, 127.7, 123.5, 122.6, 119.3, 114.9, 111.6, 80.3, 55.9, 55.8, 45.3, 32.6, 32.5, 24.2, 23.8, 10.9; HPLC (Waters Nova-Pak/EC 18 column, 3.9 x 150mm, 4micron, 1mL/min, 240nm, 50/50, CH₃CN/0.1% H₃PO₄) 8 min, 100%.

Example 15

3-(1-Oxoisoindoline)-3-(3-cyclopentyloxy-4-methoxyphenyl)-propionic Acid

A stirred solution of phthalic dicarboxaldehyde (0.67 g, 5.00 mmol) and 3-amino-3-(3-cyclopentyloxy-4-methoxyphenyl)-propanoic acid (1.40 g, 5.01 mmol) in 20 mL of glacial acetic acid under nitrogen was heated to reflux for 5 minutes. The stirred reaction then was allowed to cool to room temperature overnight. The resulting yellow brown solution was concentrated in vacuo and the solid which formed slurried in ethyl acetate (25 mL). The slurry was filtered and the solid dried in vacuo to afford 1.52 g (77%) of the product as a white powder: mp 161-163°C; ¹H NMR (dmsO-D₆/ TMS) _ 12.33 (br s, 1 H, COOH), 7.75-7.4 (m, 4 H, Ar), 7.05-6.8 (m, 3 H, Ar), 5.66 (app. t, J = 7.9 Hz, 1 H), 4.75 (m, 1 H), 4.51 (d, J = 17.7 Hz, 1 H), 4.11 (d, J = 17.7 Hz, 1 H), 3.71 (s, 3 H), 3.12 (m, 2 H), 1.95-1.45 (m, 8 H); ¹³C NMR (dmsO-D₆/ TMS) _ 171.8, 149.1, 146.8, 141.6, 132.1, 131.5, 131.3, 127.8, 123.4, 122.8, 119.2, 114.0, 112.2, 79.4, 55.5, 51.0, 46.3, 36.7, 32.1, 32.0, 23.4. Anal. Calcd for C₂₃H₂₅NO₅. Theory: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.59; H, 6.35; N, 3.44.

Example 16

Methyl 3-(1-oxoisoindoline)-3-(3-cyclopentyloxy-4-methoxyphenyl)propionate.

To a stirred suspension of 3-(1-oxoisoindoline)-3-(3-cyclopentyloxy-4-methoxyphenyl)propionic acid (0.758 g, 1.92 mmol) in 10 mL of methanol cooled in an ice bath and under nitrogen was added 0.3 mL of thionyl chloride. After stirring for 15 minutes, the mixture was allowed to warm to room

temperature and stirred overnight. The solvent was evaporated and the residue dissolved in methylene chloride and washed with saturated aqueous sodium bicarbonate solution and brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, 1/9 ethyl acetate/methylene chloride) to afford 0.6 g of the product which was stirred in hexane. The slurry was filtered to afford 0.32 g of the product as a white solid: mp 94.5-95.5°C; ¹H NMR (CDCl₃/ TMS) 7.85 (d, J = 6.7 Hz, 1 H, Ar), 7.55-7.3 (m, 3 H, Ar), 7.0-6.75 (m, 3 H), 5.92 (dd, J = 9.1, 7.0 Hz, 1 H), 4.74 (m, 1 H), 4.37 (d, J = 16.7 Hz, 1 H), 4.07 (d, J = 16.7 Hz, 1 H), 3.82 (s, 3 H), 3.64 (s, 3 H), 3.23 (dd, J = 9.1, 15.0 Hz, 1 H), 3.10 (dd, J = 9.1, 15.0 Hz, 1 H), 2.05-1.45 (m, 8 H); ¹³C NMR (CDCl₃/ TMS) 170.9, 149.8, 147.8, 141.3, 132.6, 131.3, 131.0, 127.9, 123.8, 122.7, 119.0, 114.6, 111.8, 80.5, 56.0, 52.0, 51.7, 46.6, 40.0, 32.7, 32.7, 24.0. Anal. Calcd for C₂₄H₂₇NO₅. Theory: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.07; H, 6.63; N, 3.34.

20

Example 17

Tablets, each containing 50 milligrams of active ingredient, can be prepared in the following manner:

Constituents (for 1000 tablets)

25	active ingredient	50.0 grams
	lactose	50.7 grams
	wheat starch	7.5 grams
	polyethylene glycol 6000	5.0 grams
	talc	5.0 grams
30	magnesium stearate	1.8 grams
	demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, the lactose, the talc, the magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 milliliters of water. The resulting paste is added to the pulverulent sub-

stances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter which are concave on both sides.

Example 18

Tablets, each containing 100 milligrams of active ingredient, can be prepared in the following manner:

10	<u>Constituents</u> (for 1000 tablets)	
	active ingredient	100.0 grams
	lactose	100.0 grams
	wheat starch	47.0 grams
	magnesium stearate	3.0 grams

15 All the solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, the lactose, the magnesium stearate and half of the starch then are mixed. The other half of the starch is suspended in 40 milliliters of water and this suspension is added to 100
20 milliliters of boiling water. The resulting paste is added to the pulverulent substances and the mixture is granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 6 mm diameter
25 which are concave on both sides.

Example 19

Tablets for chewing, each containing 75 milligrams of active ingredient, can be prepared in the following manner:

Composition (for 1000 tablets)

5	active ingredient	75.0 grams
	mannitol	230.0 grams
	lactose	150.0 grams
	talc	21.0 grams
10	glycine	12.5 grams
	stearic acid	10.0 grams
	saccharin	1.5 grams
	5% gelatin solution	q.s.

All the solid ingredients are first forced through a
15 sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated with the addition of gelatin solution, forced through a sieve of 2 mm mesh width, dried at 50°C and again forced through a sieve of 1.7 mm mesh width. The active
20 ingredient, the glycine and the saccharin are carefully mixed, the mannitol, the lactose granulate, the stearic acid and the talc are added and the whole is mixed thoroughly and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking groove on the upper side.

Example 20

Tablets, each containing 10 milligrams of active ingredient, can be prepared in the following manner:

Composition (for 1000 tablets)

30	active ingredient	10.0 grams
	lactose	328.5 grams
	corn starch	17.5 grams
	polyethylene glycol 6000	5.0 grams
	talc	25.0 grams
35	magnesium stearate	4.0 grams
	demineralized water	q.s.

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Then the active ingredient, lactose, talc, magnesium stearate and half of the starch are intimately mixed. The other half of the starch is suspended in 65 milliliters of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 milliliters of water. The resulting paste is added to the pulverulent substances, and the whole is mixed and granulated, if necessary with the addition of water. The granulate is dried overnight at 35°C, forced through a sieve of 1.2 mm mesh width and compressed to form tablets of approximately 10 mm diameter which are concave on both sides and have a breaking notch on the upper side.

Example 21

Gelatin dry-filled capsules, each containing 100 milligrams of active ingredient, can be prepared in the following manner:

Composition (for 1000 capsules)

active ingredient	100.0 grams
microcrystalline cellulose	30.0 grams
sodium lauryl sulphate	2.0 grams
magnesium stearate	8.0 grams

The sodium lauryl sulphate is sieved into the active ingredient through a sieve of 0.2 mm mesh width and the two components are intimately mixed for 10 minutes. The microcrystalline cellulose is then added through a sieve of 0.9 mm mesh width and the whole is again intimately mixed for 10 minutes. Finally, the magnesium stearate is added through a sieve of 0.8 mm width and, after mixing for a further 3 minutes, the mixture is introduced in portions of 140 milligrams each into size 0 (elongated) gelatin dry-fill capsules.

Example 22

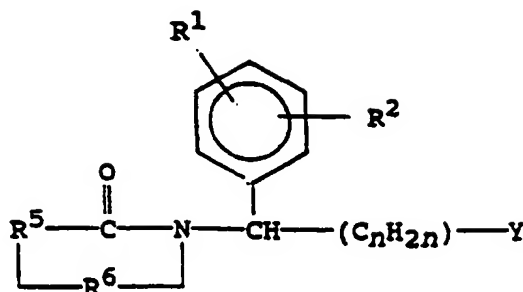
A 0.2% injection or infusion solution can be prepared, for example, in the following manner:

5	active ingredient	5.0 grams
	sodium chloride	22.5 grams
	phosphate buffer pH 7.4	300.0 grams
	demineralized water	to 2500.0 mL

10 The active ingredient is dissolved in 1000 milliliters of water and filtered through a microfilter or slurried in 1000 mL of H₂O. The buffer solution is added and the whole is made up to 2500 milliliters with water. To prepare dosage unit forms, portions of 1.0 or 2.5 milliliters each are introduced into glass ampoules (each containing respectively 2.0 or 5.0 milligrams of active ingredient).

What is claimed is:

1. A compound of the formula:



in which:

one of R^1 and R^2 is R^3-X- and the other is hydrogen, nitro, cyano, trifluoromethyl, carbo(lower)alkoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, lower alkyl, alkylamino, lower alkoxy, halo, HF_2CO , F_3CO or R^3-X- ;

R^3 is monocycloalkyl, bicycloalkyl, benzocycloalkyl of up to 18 carbon atoms, tetrahydropyran, or tetrahydrofuran;

X is a carbon-carbon bond, $-CH_2-$, $-O-$ or $-N=$;

R^5 is: (i) o-phenylene, unsubstituted or substituted with 1 or more substituents each selected independently from nitro, cyano, halo, trifluoromethyl, carbo(lower)alkoxy, acetyl, or carbamoyl, unsubstituted or substituted with lower alkyl, acetoxo, carboxy, hydroxy, amino, lower alkylamino, lower acylamino, aminoalkyl, or lower alkoxy; (ii) the vicinally divalent residue of pyridine, pyrrolidine, imidazole, naphthalene, or thiophene, wherein the divalent bonds are on vicinal ring carbon atoms; (iii) a vicinally divalent cycloalkyl or cycloalkenyl of 4-10 carbon atoms, unsubstituted or substituted with 1 or more substituents each selected independently from the group consisting of nitro, cyano, halo, trifluoromethyl, carbo(lower)alkoxy, acetyl, carbamoyl, acetoxo, carboxy, hydroxy, amino, lower alkylamino, lower alkyl, lower alkoxy, or phenyl; (iv) vinylene di-substituted with lower alkyl; or (v)

1 ethylene, unsubstituted or monosubstituted or disubsti-
2 tuted with lower alkyl;
3 R^6 is $-CO-$, $-CH_2-$, or $-CH_2CO-$;
4 Y is $-COZ$, $-CPN$, $-OR^8$, lower alkyl, or aryl;
5 Z is $-NH_2$, $-OH$, $-NHR$, $-R^9$, or $-OR^9$;
6 R^8 is hydrogen or lower alkyl;
7 R^9 is lower alkyl or benzyl; and,
8 n has a value of 0, 1, 2, or 3.

9 2. A compound according to claim 1 wherein one of R^1 and R^2 is
10 R^3-O- and the other is lower alkyl, lower alkoxy, or R^3-O- ;
11 R^3 is cyclic or bicyclic alkyl of up to 10 carbon atoms or
12 tetrahydrofuran;
13 R^5 is o-phenylene, unsubstituted or substituted with 1 or
14 more substituents each selected independently from
15 nitro, cyano, halo, trifluoromethyl, carbethoxy, car-
16 bomethoxy, carbopropoxy, acetyl, carbamoyl, or carbamoyl
17 substituted with alkyl of 1 to 3 carbon atoms, acetox-
18 y, carboxy, hydroxy, amino, amino substituted with an alkyl
19 of 1 to 3 carbon atoms, alkyl of 1 to 4 carbon atoms,
20 alkoxy of 1 to 4 carbon atoms;
21 R^6 is $-CO-$ or $-CH_2-$;
22 Y is $-COZ$ or lower alkyl;
23 Z is $-NH_2$, $-OH$, $-NHR$, $-R^9$, or $-OR^9$;
24 R^9 is alkyl or benzyl; and
25 n has a value of 1 or 2.

26 3. A compound according to claim 1 wherein R^5 is o-phenylene,
27 unsubstituted or substituted with 1 or more substituents
28 each selected independently from nitro, cyano, halo,
29 trifluoromethyl, carbo(lower)alkoxy, acetyl, or carbamoyl,
30 unsubstituted or substituted with lower alkyl, acetox-
31 y, carboxy, hydroxy, amino, lower alkylamino, lower acylamino,
32 aminoalkyl or lower alkoxy;
33 R^1 is lower alkoxy;
34 R^3 is monocycloalkyl of up to 10 carbon atoms;
35 R^6 is $-CO-$;
36 Y is $-COZ$ or $-CPN$;
37 Z is $-NH_2$, $-OH$, or $-O(\text{lower alkyl})$; and

- 1 n has a value of 0 1.
- 2 4. A compound selected from the group consisting of 3-phthal-
3 imido-3-(3-cyclopentyloxy-4-methoxyphenyl)propionic acid,
4 3-phthalimido-3-(3-cyclopentyloxy-4-methoxyphenyl)propion-
5 amide, methyl 3-phthalimido-3-(3-cyclopentyloxy-4-methoxy-
6 phenyl)propionate, methyl 3-phthalimido-3-(3-(exo-bicyclo-
7 [2.2.1]hept-2-yloxy)-4-methoxyphenyl)propionate, methyl 3-
8 phthalimido-3-(3-cyclopentyloxy-4-methoxyphenyl)propionate,
9 3-phthalimido-3-(3-cyclopentyloxy-4-hydroxyphenyl)propionic
10 acid, 3-phthalimido-3-(3-cyclohexyloxy-4-
11 methoxyphenyl)propionic acid, 3-phthalimido-3-(3-(bicyclo-
12 [3.2.1]oct-2-yloxy)-4-methoxyphenyl)propionic acid, 3-
13 phthalimido-3-(3-indan-2-yloxy-4-methoxyphenyl(propionic
14 acid, 3-phthalimido-3-(3-(endo-benzobicyclo[2.2.1]hept-2-
15 yloxy)-4-methoxyphenyl)propionic acid, 3-phthalimido-3-(3-
16 cyclopentyloxy-4-hydroxyphenyl)propionamide, 3-phthalimido-
17 3-(3-cyclohexyloxy-4-methoxyphenyl)propionamide, 3-
18 phthalimido-3-(3-(endo-bicyclo[2.2.1]hept-2-yloxy)-4-
19 methoxyphenyl)propionamide, 3-phthalimido-3-(3-(bicyclo-
20 [2.2.2]oct-2-yloxy)-4-methoxyphenyl)propionamide, 3-
21 phthalimido-3-(3-(bicyclo[3.2.1]oct-2-yloxy)-4-
22 methoxyphenyl)propionamide, 3-phthalimido-3-(3-indan-2-
23 yloxy-4-methoxyphenyl(propionamide, and 3-phthalimido-3-(3-
24 (endo-benzobicyclo[2.2.1]hept-2-yloxy)-4-meth-
25 oxyphenyl)propionamide.
- 26 5. The method of inhibiting phosphodiesterase in a mammal
27 which comprises administering thereto an effective amount
28 of a compound of Claim 1.
- 29 6. The method of inhibiting TNF α in a mammal which comprises
30 administering thereto an effective amount of a compound of
31 Claim 1.
- 32 7. The method of inhibiting NF κ B activation in a mammal which
33 comprises administering thereto an effective amount of a
34 compound of Claim 1.

- 1 8. A pharmaceutical composition comprising an amount of a com-
- 2 pound according to claim 1 effective upon single or mul-
- 3 tiple dosage to inhibit phosphodiesterase.

INTERNATIONAL SEARCH REPORT

Int. Patent Application No.
PCT/US 96/20616

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D209/48 A61K31/40 C07D209/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 01348 A (CELGENE CORPORATION) 12 January 1995 see claims 26-31,42-55 ---	1,5
A	WO 94 12461 A (PFIZER INC.) 9 June 1994 see claims ---	1,5
P,A	WO 96 20926 A (CELGENE CORPORATION) 11 July 1996 see claims -----	1,5

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

29 April 1997

Date of mailing of the international search report

20 -05- 1997

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+ 31-70) 340-3016

Authorized officer

Van Bijlen, H

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 96/20616

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 5-7 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 96/20616

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9501348 A	12-01-95	AU 7216794 A	24-01-95
		CA 2166315 A	12-01-95
		CZ 9600010 A	16-10-96
		EP 0706521 A	17-04-96
		FI 956362 A	26-02-96
		JP 9500872 T	28-01-97
		PL 312386 A	15-04-96
		SK 166595 A	08-01-97
		US 5463063 A	31-10-95
		US 5605914 A	25-02-97

WO 9412461 A	09-06-94	AU 673569 B	14-11-96
		AU 5539694 A	22-06-94
		CA 2150812 A	09-06-94
		CN 1094028 A	26-10-94
		CZ 9501417 A	15-11-95
		EP 0672031 A	20-09-95
		FI 935379 A	03-06-94
		HU 65928 A	28-07-94
		JP 8501318 T	13-02-96
		NO 952178 A	01-08-95
		NZ 257955 A	28-05-96
		PL 309257 A	02-10-95
		ZA 9308978 A	01-06-95

WO 9620926 A	11-07-96	AU 4246396 A	24-07-96
